REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-5, 7, 9-17 and 19-47 are in this case. Claims 22-45 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-5, 7, 9-17, 19-21 and 46-47 have been rejected. Claims 3-4 and 15 have now been canceled. Claims 1 and 12 have now been amended. New claims 48-69 have now been added.

35 U.S.C. § 103(a) Rejections - U.S. Pat. No. 5,806,529 in view of Bachar-Lustig et al. or Mobest et al. or Vavrova et al.

The Examiner has rejected claims 1-5, 7, 9-17, 19-21, and 46-47 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,806,529 (hereinafter "the '529 patent") in view of Bachar-Lustig *et al.*, or Mobest *et al.*, or Vavrova *et al.* The Examiner's rejections are respectfully traversed. Claims 1 and 12 have now been amended. Claims 3-4 and 15 have now been canceled. New claims 48-69 have now been added.

The Examiner contends that the '529 patent teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPCs from an allogeneic donor, but concedes that this patent does not teach culturing of the HPCs *ex-vivo* under conditions suitable for inducing or enhancing veto activity. The Examiner further contends that Bachar-Lustig *et al.*, Mobest *et al.*, and Vavrova *et al.* each teach culturing of HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs, and for inducing differentiation of said HPCs into CD33+ myeloid phenotype cells using the same culturing conditions as those disclosed in the instant specification. The Examiner additionally contends that Mobest *et al.* and Vavrova *et al.* each teach *ex-vivo* expansion of CD34+ HPCs that differentiate into CD33+ myeloid phenotype cells offering the possibility of various non-tolerance inducing auxiliary benefits related to therapeutic transplantation of CD34+ cells.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made that CD34+ HPCs obtained and grown under the conditions putatively taught by any one of the secondary reference

teachings would be induced to differentiate into myeloid CD33+ cells with the same functional property as HPCs recited in the instant claims absent a showing of unobvious property.

'529 Patent in view of Bachar-Lustig et al.:

With respect to the rejection relating to the '529 patent in view of Bachar-Lustig *et al.*, the Examiner contends that the latter reference teaches that it is possible to culture HPCs under growth conditions suitable for inducing or enhancing tolerance-inducing activity of CD34+ cells by expanding *in-vitro* the CD34+ cells and using them for transplantation (Abstract and page 3220 in particular). The Examiner particularly contends that Bachar-Lustig *et al.* teaches growth conditions which are the same as those taught by the instant specification. The Examiner concludes that it would have been obvious to one skilled in the art at the time the invention was made that culturing CD34+ HPCs under conditions taught by Bachar-Lustig et al. could be used to generate myeloid CD33+ cells with the same functional property as the cultured HPCs taught by the instant invention.

Applicant wishes to respectfully point out that, in clear contradiction with the Examiner's contention, at no point does Bachar-Lustig *et al.* teach that it is possible, to culture HPCs under growth conditions suitable for inducing/enhancing their tolerance inducing activity. The Examiner has particularly directed Applicant to page 3220 and to the Abstract in support of this contention. Applicant wishes to respectfully point out that, in fact, page 3220 (third paragraph) clearly and unambiguously disproves this contention, in accordance with the quote "...*if it were possible to expand the veto cells within the CD34+ progenitor cell fraction.*", which clearly signifies that Bachar-Lustig *et al.* does not teach methods of culturing CD34+ cells for expansion of veto cells, but rather that such a methods are clearly unknown in the art. In accordance with such teachings of Bachar-Lustig *et al.* that it is not possible to culture CD34+ cells for expansion of veto cells, the Abstract of this reference does not, in very sharp contrast to the Examiner's contention, in any way teach, suggest or demonstrate that it is possible to culture HPCs under growth conditions suitable for inducing or enhancing tolerance-inducing activity of CD34+ cells by expanding CD34+ in-vitro for transplantation. Applicant wishes to respectfully and emphatically point out that at no point does Bachar-Lustig *et al.* directly or indirectly refer to myeloid cells of any type, including CD33+ cells. On

the basis of such arguments alone, Applicant is of the vigorous opinion that it could not possibly have been obvious to the ordinarily skilled artisan at the time the instant invention was made to combine the teachings of the '529 patent with Bachar-Lustig *et al.* so as to obtain a method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipient comprising a step of ex-vivo culturing HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs and inducing differentiation of said HPCs into CD33+ myeloid phenotype cells prior to transplantation of the transplant. Since Bachar-Lustig *et al.* clearly do not teach any culturing conditions whatsoever, nor mention any type of myeloid cells, Applicant wishes to respectfully point out that the Examiner's contention that Bachar-Lustig *et al.* teaches the same culturing conditions as the instant invention so as to enable generation of myeloid CD33+ cells having tolerance-inducing activity is simply unfounded.

Still further, Applicant wishes to respectfully point out that Bachar-Lustig *et al.* teach the culturing of Sca1+Lin– mouse cells (Bachar-Lustig *et al.*, Title, Abstract and throughout reference) which are not homologous in critical respects to the purified human CD34+ cells whose culturing is taught by the instant invention (specification, page 41, section entitled "Peripheral blood progenitor cell (PBPC) collection, processing and CD34+ purification", sentence starting at line 10 in particular; and page 24, third paragraph). Indeed, it was well known to one of ordinary skill in the art at the time the invention was made that Sca1+Lin– mouse cells are composed of both CD34+ and CD34 negative cells, and in this critical respect represent a population which is clearly non-homologous to the purified human CD34+ cells taught by the instant invention (refer to enclosed abstracts of; Masuhara *et al.*; Morel *et al.*; Nakauchi *et al.*; Osawa *et al.*; and Shimomura *et al.*), as taught by the instant invention. As such, even if culturing of mouse Sca1+Lin– cells to generate expanded veto cells had indeed been taught or demonstrated in Bachar-Lustig *et al.*, one of ordinary skill in the art would in any case not have a reasonable expectation of success in applying such hypothetical teachings towards expanding veto cells by culturing purified CD34+ cells in the absence of CD34 negative cells. The ordinarily skilled artisan considering applying such hypothetical teachings to purified human CD34+ cells, as taught by the instant invention, would have expected an even greater lack of reasonable expectation of success due to potential variation between the

human and mouse biological systems. On the basis of such arguments alone as well, Applicant is of the very strong opinion that it would not have been obvious to the ordinarily skilled artisan at the time the instant invention was made to combine the teachings of the '529 patent with those of Bachar-Lustig *et al.* to obtain a method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipient comprising a step of *ex-vivo* culturing HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs and inducing differentiation of said HPCs into CD33+ myeloid phenotype cells prior to transplantation of the transplant.

Applicant is of the opinion that in combination, the arguments provided above overwhelmingly demonstrate that it would not have been obvious to the ordinarily skilled artisan at the time the instant invention was made to combine the teachings of the '529 patent with those of Bachar-Lustig *et al.* to obtain the instant invention.

Nevertheless, in the interest of expediting prosecution of the instant invention, Applicant currently elects to add New claims 48 and 59, depending from claims 1 and 12, respectively, each including the limitation of the donor and/or the recipient being a human; and New claims 49 and 60, depending from claims 1 and 12, respectively, each including the limitation of the cultured HPCs being obtained by culturing substantially purified CD34+ cells. Specification support for such amendments is provided in the context of the argumentation set forth above.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 103(a) rejections relating to the '529 patent in view of Bachar-Lustig *et al.*

'529 Patent in view of Mobest et al. or Vavrova et al.:

With respect to the rejections relating to the '529 patent in view of Mobest *et al.* or Vavrova *et al.*, the Examiner contends that the latter references teach *ex-vivo* expansion of human CD34+ HPCs under conditions suitable for inducing differentiation of said cells into CD33+ myeloid phenotype cells. The Examiner additionally contends that the growth conditions taught by Mobest *et al.* or Vavrova *et al.* are the same as those taught by the instant invention. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made that CD34+ HPCs grown under the conditions taught by Mobest *et al.* or Vavrova *et al.* would be induced to differentiate into myeloid CD33+ cells with the

same functional property as the cultured HPCs taught by the instant invention.

Applicant firstly wishes to respectfully point out that the growth conditions taught by the instant specification and cited by claims 1 and 12, and those taught by Mobest *et al.* or Vavrova *et al.* are in fact clearly and significantly different, in very sharp contrast to the Examiner's contention that these are the same.

The growth conditions taught by the instant specification involve a culture medium containing fetal calf serum (FCS), Flt3-ligand, stem cell factor (SCF) and thrombopoietin (TPO).

In very sharp contrast, Mobest *et al.* teach growth conditions involving a serum-free culture medium containing a very large number of supplements (page 342, under Cell Culture) which are not added to the growth media taught by the instant invention. In particular Mobest *et al.* teach culturing conditions which include such highly potent and pleiotropic growth/differentiation factors as IL-1beta, IL-3, and IL-6 (see Abstract), but which do not include the highly distinct, potent and pleiotropic set of growth/differentiation factors FCS, SCF, Flt3-ligand, and TPO as taught by the instant specification (see page 44, second paragraph).

Also in very sharp contrast to the culturing conditions taught by the instant invention, Vavrova *et al.* teaches growth conditions involving a culture medium containing such highly potent growth/differentiation factors as IL-11 and IL-3 which are not included in the growth conditions taught by the instant specification. The potent synergistic effects of varying cytokine supplementations involving IL-11 and/or IL-3 is emphatically demonstrated at page 110, Figure 3 of Vavrova *et al.* Moreover, unlike those taught by the instant specification, the growth conditions taught by Vavrova *et al.* do not include a culture medium supplemented with the potent growth/differentiation factors Flt3-ligand, and TPO.

Since the culturing conditions taught by the instant specification and Mobest *et al.* or Vavrova *et al.* include such clearly distinct, complex and potent mixtures of growth/differentiation factors, Applicant is of the opinion that the ordinarily skilled artisan would consider that culturing HPCs using the culturing conditions taught by Mobest *et al.* or Vavrova *et al.* could not reasonably be expected to generate a cultured cell population necessarily having the same or similar tolerance-inducing capacity as when culturing HPCs under the very different culturing conditions taught by the instant invention.

Applicant wishes to emphasize that Mobest *et al.* makes a clear distinction between the culture conditions taught by the instant invention which employ FCS and those taught by Mobest *et al.* which are serum-free. The first sentence of the Abstract of Mobest *et al.* cited by the Examiner clearly indicates that the teachings of Mobest *et al.* are drawn to the advantages of HPC culture media which avoid serum supplementation. Furthermore, the Abstract of Mobest *et al.* cited by the Examiner recites: "*Addition of... FCS to SFM-1* (the medium taught by Mobest *et al.* for culturing HPCs) *resulted in inferior cell amplification and CFC formation... indicating that the components used in SFM-1 could replace exogenous serum*". Hence, not only does Mobest *et al.* clearly teach that the culturing conditions of the instant invention and those taught by Mobest *et al.* are critically different, but by specifically referring to the disadvantages of FCS supplementation, actually teaches away from using the culture conditions taught by the instant specification which do include such supplementation. Indeed, it was known in the prior art that culturing of CD34+ cells led to significantly divergent cultured cell populations depending on whether the culture media employed were serum-supplemented or non–serum-supplemented (refer, for example, to enclosed Abstracts of: Donaldson *et al.*; Mellado-Damas *et al.*).

The highly divergent characteristics of the cultured cells taught by Mobest *et al.* and those taught by the instant invention, resulting from the highly divergent culturing conditions thereof, are indeed clearly apparent in the cultured cell populations respectively generated. For example, the culturing conditions taught by the instant invention lead to cultured cells which are 83.5 % CD33+, 48.6 % CD34+, 33 % CD33+CD34+, 79 % CD13+, 80 % CD4low, and which do not include CD8+, CD20+ and CD56+ cells (specification, page 49, sentence starting at line 14 to end of paragraph: the figure of 83.5 % CD33+ cells is obtained by adding 33 % CD33+CD34+ cells and 50.5 % CD33+CD34– cells; and the figure of 48.6 % CD34 cells is obtained by adding 15.6 % CD34+CD33+ cells and 33 % CD33+CD34+ cells).

In sharp contrast, however, the culturing conditions taught by Mobest *et al.* or Vavrova *et al.* generate a significantly lower percentage of CD33+ cells than the 83.5 % obtained, and a significantly lower percentage of CD34+ cells than the 48.6 % obtained, according to the culturing conditions of the instant invention. Namely, in

the case of Mobest *et al.*, the percentage of CD33+ cells obtained is on average approximately 35-40 % (see Mobest *et al.*, page 345, Figure 3), and in the case of Vavrova *et al.*, the percentage of CD33+ cells obtained is 59 % (Vavrova *et al.*, Abstract). With respect to CD34+ cells, in the case of Mobest *et al.*, essentially no CD34+ cells are obtained (Mobest *et al.*, page 345, Figure 3), and in the case of Vavrova *et al.*, only 11.8 % of the cells obtained are CD34+, as opposed to the approximately 50 % of the cells of the instant invention being CD34+.

Applicant wishes to particularly point out that, critically, the culturing conditions taught by Mobest *et al.* do not generate any CD33+CD34+ cells (page 345, Figure 3). Similarly, in the case of Vavrova *et al.*, even assuming that all CD34+ cultured cells obtained (11.8 % of the total), are CD33+ (not shown), such culturing conditions can only generate a cultured cell population composed of a maximum of 11.8 % of CD33+CD34+ cells. This stands in sharp contrast with the 33 % of CD33+CD34+ cultured cells obtained according to the teachings of the present invention. Furthermore, neither Mobest *et al.* nor Vavrova *et al.* demonstrates that the cultured cells obtained are free of CD8+, CD20+ and/or CD56+ cells, as is the case according to the teachings of the present invention. The ordinarily skilled artisan would therefore conclude that the cultured cell populations obtained according to Mobest *et al.* or Vavrova *et al.* would have potentially highly divergent functional characteristics, such as those involving veto capacities. In particular, the ordinarily skilled artisan would consider that the very early stage CD33+CD34+ myeloid cells representing one-third of all cultured cells generated according to the culturing conditions of the present invention, but which are not produced at all according to the teachings of Mobest *et al.*, or which are produced, in a theoretical maximum, in an approximately three-fold lower percentage according to the teachings of Vavrova *et al.*, respectively, would quite possibly, but unpredictably, possess unique functional attributes, such as tolerance-inducing capacities, relative to the cultured cells taught by these references. One of ordinary skill in the art would draw similar conclusions with respect to CD34+ cells in light of the significantly lower percentages of such cells obtained according to the culturing conditions of Mobest *et al.* or Vavrova *et al.* as compared to those of the instant invention.

Applicant is therefore of the very firm opinion that it would not have been obvious to the ordinarily skilled artisan at the time the instant invention was made that

it would be possible to generate the tolerance-inducing cells of the instant invention according to the teachings of Mobest *et al.* or Vavrova *et al.* without undue experimentation.

Applicant wishes to respectfully point out that neither the '529 patent nor Mobest *et al.*, nor Vavrova *et al.* suggests, demonstrates nor teaches cells which can facilitate engraftment of transplants which are of non-bone marrow origin and non-syngeneic with the recipient. More particularly, neither Mobest *et al.* nor Vavrova *et al.* demonstrates, suggests or teaches cultured cells which can facilitate engraftment of any type of transplant, and the '529 patent does not demonstrate, suggest or teach cells which can facilitate engraftment of non-bone marrow-derived grafts which are non-syngeneic with the recipient.

In light of the clear absence of such teachings, Applicant is of the very firm opinion that the ordinarily skilled artisan at the time the invention was made would not expect with a reasonable degree of confidence that administering to a recipient cultured cells according to Mobest *et al.* or Vavrova *et al.*, whether in the presence of absence of CD34+ bone marrow cells derived from a donor according to the teachings of the '529 patent, would necessarily lead to engraftment of such cultured cells or would necessarily even allow engraftment of the non-cultured CD34+ bone marrow cells as would be the case if these were administered alone. It was very well known in the art at the time the invention was made that, when cultured, CD34+ cells have a clear and consistent tendency to undergo significant phenotypic alterations, in particular involving dedifferentiation (refer, for example, to enclosed Title of Von Laer *et al.*; and of Abstracts of: Denning-Kendall *et al.*; Bennaceur-Griscelli *et al.*). One of ordinary skill in the art would therefore assume that such phenotypic alterations, particularly those involving dedifferentiation from the optimally tolerogenic undifferentiated state, could quite possibly, yet unpredictably, lead to immunologic host responses involving impairment of engraftment of the cultured cells and/or of the non-cultured CD34+ bone marrow cells themselves. Applicant wishes to emphatically point out that it was the experiments disclosed in the instant specification which taught for the first time the unpredictable fact that cultured stem cells could generate cultured cells displaying retention and enhancement of veto capacity relative to non-cultured stem cells. Therefore, on the basis of these arguments alone, Applicant is of the very strong opinion that it would not have been

obvious at the time the instant invention was made to combine the teachings of the '529 patent and those of Bachar-Lustig *et al.* or Mobest *et al.* or Vavrova *et al.* to obtain the instant invention.

Applicant wishes to further point out that, critically, in the case of Vavrova *et al.*, the CD34+ cells which are cultured are derived from high-risk breast cancer patients receiving intensive chemotherapy, following administration thereto of epirubicin and cyclophosphamide (Vavrova *et al.*, Title itself and page 106, Column 2, "Mobilization procedure"). In very sharp and highly significant contrast, the CD34+ cells which are cultured according to the teachings of the present invention are derived from healthy individuals (specification, page 41, line 5). It was well known to those of skill in the art at the time the instant invention was made that cyclophosphamide is a potent myelotoxic mutagen (refer, for example, to enclosed Abstract of Fraiser *et al.*; and Douay *et al.*), and similarly that epirubicin is also a potent myelotoxin (refer, for example, to enclosed Abstract of Ganzina *et al.*; and Okunewick *et al.*). Furthermore, it was well known in the art that cancer patients often exhibit significant malignancy-induced myelosuppression (refer, for example to enclosed Abstract of Rostad; Wojtowicz-Praga; and Pollock and Roth). Thus, in light of the well known myelotoxicity of cyclophosphamide and epirubicin, and of the potentially significantly myelosuppressed status of individuals affected with aggressive malignancies such as high-risk breast cancer, Applicant is of the very firm opinion that one of ordinary skill in the art would expect that the CD34+ cells derived from the donors taught by Vavrova *et al.* would be potentially significantly abnormal. As such the ordinarily skilled artisan would certainly not expect to have a reasonable expectation of success in obtaining cultured cells having similar functionalities, such as tolerance inducing capacities, when culturing CD34+ cells derived from the donors taught by Vavrova *et al.*, as compared to the healthy donors (i.e. non-cancerous, nor undergoing intensive myelotoxic chemotherapy) taught by the instant invention. On the basis of such arguments alone, Applicant is of the very strong opinion that one of ordinary skill in the art would not be motivated to combine the teachings of Vavrova *et al.* with those of the '529 patent to obtain the instant invention.

The Examiner additionally contends that Mobest *et al.* teaches cultured cells offering the possibility of additional graft manipulation steps such as depletion or elimination of contaminating tumor cells in autologous grafts, amplification of bone

marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells (page 341 in particular), and that Vavrova *et al.* teaches ex-vivo expansion of HPC which would benefit studies including accelerated engraftment, reduced risk of infection, smaller stem cell harvest and improved effectiveness of genetically modified stem cells. The Examiner concludes that such possibilities provide motivation to the ordinarily skilled artisan for combining the teachings of the '529 patent and those of Mobest *et al.* or Vavrova *et al.* for making the instant invention.

Applicant wishes to respectfully point out that such putative possibilities afforded by Mobest *et al.* or Vavrova *et al.* are strictly limited to hematopoietic transplants. In very sharp, and critically significant, contrast the teachings of the instant invention are drawn to all types of transplants, including those which are of non-hematopoietic origin (specification, page 23, sentence starting at last line to page 25 line 16). As such, the ordinarily skilled artisan at the time the invention was made would clearly not have been motivated to combine the teachings of the '529 patent and those of Mobest *et al.* or Vavrova *et al.* to obtain the instant invention which provides for facilitation of engraftment of non-hematopoietic grafts which are non-syngeneic with the recipient thereof.

Applicant is of the strong opinion that in combination, the arguments provided above overwhelmingly indicate that it would not have been obvious to the ordinarily skilled artisan at the time the instant invention was made to combine the teachings of the '529 patent with those of Mobest *et al.* or Vavrova *et al.* to obtain a method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipient comprising a step of culturing HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs and inducing differentiation of said HPCs into CD33+ myeloid phenotype cells prior to transplantation of the transplant.

Nevertheless, in the interest of expediting prosecution of the instant invention, Applicant currently elects to amend independent claims 1 and 12, and thereby all claims dependent therefrom, to include the limitation of the donor being allogeneic or xenogeneic with the recipient. Also in the interest of expediting prosecution of the instant invention Applicant further currently elects to make the following amendments.

(i) Adding New claims 50 and 61, depending from claims 1 and 12, respectively, each including the limitation of CD33+ cells making up at least 83.5 percent of the cultured HPC population.

(ii) Adding New claims 51 and 62, depending from claims 1 and 12, respectively, each including the limitation of CD34+ cells making up at least 48.6 percent of the cultured HPC population.

(iii) Adding New claims 52 and 63, depending from claims 1 and 12, respectively, each including the limitation of CD33+CD34+ cells making up at least 33 percent of the cultured HPC population.

(iv) Adding New claims 53 and 64, depending from claims 1 and 12, respectively, each including the limitation of CD13+ cells making up at least 79 percent of the cultured HPC population.

(v) Adding New claims 54 and 65, depending from claims 1 and 12, respectively, each including the limitation of CD4low cells making up at least 80 percent of the cultured HPC population.

(vi) Adding New claims 55 and 66, depending from claims 1 and 12, respectively, each including the limitation of the cultured HPC population being substantially free of CD8+, CD20+, and/or CD56+ cells.

(vii) Adding New claims 56 and 67, depending from claims 1 and 12, respectively, each including the limitation of the transplant being substantially of non-hematopoietic origin.

(viii) Adding New claims 57 and 68, depending from claims 1 and 12, respectively, each including the limitation of the donor not being myelosuppressed, or not being potentially myelosuppressed.

(ix) Adding New claims 58 and 69, depending from claims 1 and 12, respectively, each including the limitation of the growth conditions including supplementation with serum, fetal calf serum, Flt3-ligand, stem cell factor and/or thrombopoietin, but not including supplementation with IL-1beta, IL-3, IL-6 and/or IL-11.

Specification support for these amendments is provided in the context of the arguments set forth above.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 103(a) rejections relating to the '529 patent in view of

Mobest *et al.* or Vavrova *et al.*

In view of the above amendments and remarks it is respectfully submitted that claims 1-2, 5, 7, 9-14, 16-17, 19-21, 46, 47 and New claims 48-69 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Sol Sheinbein
Registration No. 25,457

Date: March 17, 2004.

Encl.:
A 3-months extension fee;
A response transmittal fee for added claims;
The following Abstracts:

Abstract of Bennaceur-Griscelli A. *et al.*, 1999. Blood. 94(2):529-38;

Abstract of Denning-Kendall *et al.* Br J Haematol. 1999 Jun:105(3):780-5;

Abstract of Donaldson C, Denning-Kendall P, Bradley B, Hows J., 2001. Bone Marrow Transplant. 27(4):365-71;

Abstract of Douay *et al.* Eur J Cancer. 1995;31A Suppl 1:S14-6;

Abstract of Fraiser *et al.* Drugs. 1991 Nov;42(5):781-95;

Abstract of Ganzina *et al.* Tumori. 1985 Jun 30;71(3):233-40;

Abstract of Masuhara *et al.*, 2000. Biochem Biophys Res Commun. 268:697;

Abstract of Morel *et al.*, 1996. Blood. 88:3774; Nakauchi *et al.*, 1999. Ann N Y Acad Sci. 872:57;

Abstract of Mellado-Damas N, Rodriguez JM, Carmona M, Gonzalez J, Prieto J., 1999. Leuk Res. 23(11):1035-40;

Abstract of Nakauchi *et al.*, 1999. Ann N Y Acad Sci. 872:57

Abstract of Okunewick *et al.* Process Soc Exp Biological Med. 1990 Oct; 195(1):95-9;

Abstract of Osawa *et al.*, 1996. Science. 273:242;

Abstract of Pollock RE, Roth JA. Semin Surg Oncol. 1989;5(6):414-9;

Abstract of Rostad. Oncol Nurs Forum. 1991 Mar;18(2 Suppl):7-15;

Abstract of Shimomura *et al.*, 2000. Int J Hematol. 71:33; and

Abstract of Wojtowicz-Praga S. J Immunother. 1997 May;20(3):165-77; and Title of von Laer *et al.*, 2000. Leukemia 14:947.

Blood. 1999 Jul 15;94(2):529-38.

Murine stromal cells counteract the loss of long-term culture-initiating cell potential induced by cytokines in CD34(+)CD38(low/neg) human bone marrow cells.

Bennaceur-Griscelli A, Tourino C, Izac B, Vainchenker W, Coulombel L.

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Evidence has been provided recently that shows that high concentrations of cytokines can fulfill functions previously attributed to stromal cells, such as promote the survival of, and led to a net increase in human primitive progenitors initiating long-term cultures in vitro (LTC-IC) or engrafting NOD-SCID (nonobese diabetic severe-combined immunodeficient) recipients in vivo. These data prompted us to re-evaluate whether stromal cells will further alter the properties of primitive progenitor cells exposed to cytokines. Single CD34(+)CD38(low) and CD38(neg) cells were incubated 10 days in serum-containing or serum-free medium in the presence or in the absence of murine marrow-derived stromal cells (MS-5). Recombinant human cytokines stem cell factor (SCF), pegylated-megakaryocyte growth and differentiation factor (PEG-MGDF), FLT3-L, Interleukin (IL)-3, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF) were systematically added at various concentrations (10 to 300 ng/mL). Cell proliferation and LTC-IC potential were evaluated in each clone after 10 days. A striking and consistent observation was the retention of a high LTC-IC potential in clones exposed to cytokines in the presence of stromal feeders, whereas clones exposed to cytokines alone in the absence of stromal feeders rapidly lost their LTC-IC potential as they proliferated. This was reflected both by the higher proportion of wells containing LTC-IC and by the high numbers of CFC produced after 5 weeks in clones grown with MS-5 during the first 10 days. We further showed by analyzing multiple replicates of a single clone at day 10 that MS-5 cells promoted a net increase in the LTC-IC compartment through self-renewal divisions. Interestingly, these primitive LTC-IC were equally distributed among small and large clones, as counted at day 10, indicating that active proliferation and loss of LTC-IC potential could be dissociated. These observations show that, in primitive cells, stromal cells counteract differentiation events triggered by cytokines and promoted self-renewal divisions. Furthermore, the almost identical distribution of the size of the clones with or without MS-5 suggests that proliferation and function of human primitive cells may be independently regulated by external signals, and that the former is primarily under the control of cytokines.

PMID: 10397720 [PubMed - indexed for MEDLINE]

Br J Haematol. 1999 Jun;105(3):780-5.

Related Articles, Links

Different behaviour of fresh and cultured CD34+ cells during immunomagnetic separation.

Denning-Kendall PA, Horsley H, Donaldson C, Bradley B, Hows JM.

Division of Transplantation Sciences, University of Bristol, Bristol.

In-vitro expansion of human cord blood (CB) cells could enhance peripheral blood recovery and ensure long-term engraftment of larger recipients in the clinical transplant setting. Enrichment of CD34+ cells using the MiniMACS column has been evaluated for the preparation of CB CD34+ cells before and after expansion culture. Repurification of CD34+ cells after culture would assist accurate phenotypic and functional analysis. When fresh CB mononuclear cells (MNC) were separated, the MACS positive (CD34+) fraction (90.1% pure) contained a mean (+/- SD, n = 5) of 93.0 +/- 8.0% of the eluted CD34+ cells, 99.6 +/- 0.7% of the CFU-GM and all of the eluted long-term culture-initiating cells (LTC-IC). Cord blood CD34+ cells were then cultured for 14 d with IL-3, IL-6, SCF, G-CSF and GM-CSF, each at 10 ng/ml. The total cell expansion was 2490 +/- 200-fold and the CD34+ cell expansion was 49 +/- 17-fold. The percentage of CD34+ cells present after expansion culture was 1.2 +/- 0.85%. When these cells were repurified on the MiniMACS column, the MACS positive fraction only contained 40.3 +/- 13.4% of the eluted CD34+ cells which was enriched for the mature CD34+ CD38+ subset, 24.4 +/- 8.8% of the eluted CFU-GM and 79.5 +/- 11.0% of the LTC-IC. The remaining cells were eluted in the MACS negative fraction. In conclusion, repurification of cultured CD34+ cells does not yield a representative population and many progenitors are lost in the MACS negative fraction. This can give misleading phenotypic and functional data. Cell losses may be important in the clinical setting if cultured cells were repurified for purging.

PMID: 10354147 [PubMed - indexed for MEDLINE]

Bone Marrow Transplant. 2001 Feb;27(4):365-71.

nature publishing group

The CD34(+)CD38(neg) population is significantly increased in haemopoietic cell expansion cultures in serum-free compared to serum-replete conditions: dissociation of phenotype and function.

Donaldson C, Denning-Kendall P, Bradley B, Hows J.

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Expansion of haemopoietic stem cells is proposed to combat graft failure in adult recipients following cord blood (CB) transplantation. Cultures are traditionally performed in medium containing FCS, but to transfer expansion to the clinic, 'good manufacturing practice' (GMP) standards are required. This study evaluated expansion cultures in culture bags and serum-free (SF) conditions, to comply with GMP, by analysing sub-populations of CD34(+) cells, colony-forming cells (CFC) and long-term culture initiating cells (LTC-IC). CD34(+)cell analysis has previously been used to measure clonogenic capacity and the CD34(+)CD38(neg) surface phenotype to measure primitive cell numbers. In this study, comparison of expansion in serum-replete medium with that in SF conditions demonstrated a lack of expression of CD38 on CD34(+) cells in the absence of serum. These findings must be considered in clinical studies using in vitro expansion in SF conditions, and the CD34(+)CD38(neg) phenotype should not be used to confirm maintenance, or expansion, of primitive progenitor cells.

PMID: 11313665 [PubMed - indexed for MEDLINE]

Eur J Cancer. 1995;31A Suppl 1:S14-6.

Amifostine (WR-2721) protects normal haematopoietic stem cells against cyclophosphamide derivatives' toxicity without compromising their antileukaemic effects.

Douay L, Hu C, Giarratana MC, Gorin NC.

University of Paris-Saint-Antoine Medicine School, Hopital d'enfants, Paris, France.

We compared the effects of amifostine (WR-2721) on the cytotoxicity of mafosfamide or 4-hydroperoxycyclophosphamide (4-HC) in normal marrow progenitor cells (CFU-GM) and leukaemic progenitor cells (CFU-L) during ex vivo purging for autologous bone marrow transplantation (ABMT). Mononuclear cells (MNC) were incubated with amifostine 3 mg/ml for 15 min, washed, and subsequently tested for their sensitivity to mafosfamide or 4-HC (20-200 micrograms/ 10(7) MNC/ml). The LD95 was significantly higher among amifostine-treated cells for PCM-CFU-GM in 6 of 13 patients and for 5R-CFU-GM in 4 of 10 patients ($P < 0.05$). In contrast, amifostine exhibited no protective effects upon CFU-L. The results of this study will show that amifostine protects normal late and early progenitor cells for the toxic effects of cyclophosphamide derivatives while preserving their antileukaemic effects. These results suggest that amifostine has therapeutic value as a protective agent for normal marrow progenitor cells during ex-vivo purging of bone marrow for ABMT.

PMID: 7577094 [PubMed - indexed for MEDLINE]

Drugs. 1991 Nov;42(5):781-95.

Related Articles, Links

Cyclophosphamide toxicity. Characterising and avoiding the problem.

Fraiser LH, Kanekal S, Kehrer JP.

Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas, Austin.

Cyclophosphamide, an orally active alkylating agent, is widely used to treat a variety of malignant and nonmalignant disorders. Although it has some tumour selectivity, it also possesses a wide spectrum of toxicities. The requirement of metabolic activation before cyclophosphamide exerts either its therapeutic or toxic effects is well established, but has not led to effective counter-measures. Clinically, damage to the bladder (haemorrhagic cystitis), immunosuppression (when not desired) and alopecia are the most significant toxicities associated with cyclophosphamide. Cardiotoxicity is also a possibility when very high doses are given. Preventing these toxicities has focused on modifications of the treatment regimens and, in the case of haemorrhagic cystitis, the administration of a drug which is excreted in the urine where it inactivates the bladder-toxic species. As treatment regimens for cancer become more effective in prolonging a patient's life, and as cyclophosphamide receives increasing use for nonmalignant disorders, the potential for cyclophosphamide-induced cancers, particularly in the bladder, must be recognised. Although the toxicities associated with cyclophosphamide are serious, this agent remains a highly effective drug in many situations. Research on the pathways which play an important role in activating this drug may improve our ability to target particular diseases and decrease unwanted side effects.

Publication Types:

- Review
- Review, Tutorial

Tumori. 1985 Jun 30;71(3):233-40.

Related Articles, Links

Clinical toxicity of 4'-epi-doxorubicin (epirubicin).

Ganzina F, Di Pietro N, Magni O.

Epirubicin is a new derivative of doxorubicin characterized by an improved spectrum of activity and a better therapeutic index. At equimolar doses and in comparative studies, epirubicin proved to induce less acute toxicity than doxorubicin, in particular less vomiting, hair loss and myelotoxicity. While giving a comparable response rate in randomized breast cancer studies, epirubicin also proved to be less cardiotoxic than doxorubicin. The reduced potential for cardiac toxicity of epirubicin versus doxorubicin has been shown both by functional assessment (radionuclide cinecardioangiography) and by histopathologic evaluation (endomyocardial biopsies) at equally myelosuppressive doses or at equal doses (equimolar). The lessened cardiotoxicity of epirubicin versus doxorubicin can be explained by the different pharmacokinetic and metabolic properties of these two agents: epirubicin has been found to have a more rapid pharmacokinetic plasma clearance and an additional metabolic pathway (unique glucuronidation).

PMID: 3861022 [PubMed - indexed for MEDLINE]

Biochem Biophys Res Commun. 2000 Feb 24;268(3):697-703.

Related Articles, Links

Molecular cloning of murine STAP-1, the stem-cell-specific adaptor protein containing PH and SH2 domains.

Masuhara M, Nagao K, Nishikawa M, Sasaki M, Yoshimura A, Osawa M.

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To identify the novel substrate of c-kit which is important for hematopoietic stem cell self-renewal or differentiation, CD34-low/negative, Sca-1-positive, c-kit-positive, and lineage marker-negative (CD34(low/-)Sca-1(+)c-kit(+)Lin(-)) cells were sorted by a fluorescence-activated cell sorter from mouse bone marrow cells and a yeast two-hybrid cDNA library was constructed. By screening with c-kit as bait, we cloned a novel cDNA, designed STAP-1, encoding an adaptor protein with a Pleckstrin homology domain, the Src homology 2 (SH2) domain, and a number of tyrosine phosphorylation sites. RT-PCR analysis revealed that STAP-1 expression is restricted in the bone marrow cell fraction expressing c-kit. The highest expression was observed in the CD34(low/-)Sca-1(+)c-kit(+)Lin(-) stem cell-enriched fraction. The murine myeloid cell line, M1, expressed a high level of STAP-1. However, the expression was strongly repressed in response to leukemia inhibitory factor (LIF) which induced monocytic differentiation of M1 cells, suggesting that STAP-1 is associated with the undifferentiated cell type. A two-hybrid assay indicated that STAP-1 bound not only to c-kit but also to c-fms but not to JAK2 or Pyk2. In 293 cells, STAP-1 was tyrosine-phosphorylated by activated c-kit. An in vitro binding assay suggested that the STAP-1 SH2 domain interacted with several tyrosine-phosphorylated proteins including c-kit and STAT5. These suggest that STAP-1 functions as an adaptor molecule downstream of c-kit in hematopoietic stem cells.

PMID: 10679268 [PubMed - indexed for MEDLINE]

1: Blood. 1996 Nov 15;88(10):3774-84. Related Articles, Links

Primitive hematopoietic cells in murine bone marrow express the CD34 antigen.

Morel F, Szilvassy SJ, Travis M, Chen B, Galy A.

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The CD34 antigen is expressed on most, if not all, human hematopoietic stem cells (HSCs) and hematopoietic progenitor cells, and its use for the enrichment of HSCs with repopulating potential is well established. However, despite homology between human and murine CD34, its expression on subsets of primitive murine hematopoietic cells has not been examined in full detail. To address this issue, we used a novel monoclonal antibody against murine CD34 (RAM34) to fractionate bone marrow (BM) cells that were then assayed in vitro and in vivo with respect to differing functional properties. A total of 4% to 17% of murine BM cells expressed CD34 at intermediate to high levels, representing a marked improvement over the resolution obtained with previously described polyclonal anti-CD34 antibodies. Sixty percent of CD34+ BM cells lacked lineage (Lin) markers expressed on mature lymphoid or myeloid cells. Eighty-five percent of Sca-1+Thy-1(10)Lin-/10 cells that are highly enriched in HSCs expressed intermediate, but not high, levels of CD34 antigen. The remainder of these phenotypically defined stem cells were CD34-. In vitro colony-forming cells, day-8 and -12 spleen colony-forming units (CFU-S), primitive progenitors able to differentiate into B lymphocytes in vitro or into T lymphocytes in SCID mice, and stem cells with radioprotective and competitive long-term repopulating activity were all markedly enriched in the CD34+ fraction after single-parameter cell sorting. In contrast, CD34-BM cells were depleted of such activities at the cell doses tested and were capable of only short-term B-cell production in vitro. The results indicate that a significant proportion of murine HSCs and multilineage progenitor cells express detectable levels of CD34, and that the RAM34 monoclonal antibody is a useful tool to subset primitive murine hematopoietic cells. These findings should facilitate more direct comparisons of the biology of CD34+ murine and human stem and progenitor cells.

PMID: 8916941 [PubMed - indexed for MEDLINE]

Leuk Res. 1999 Nov;23(11):1035-40.

Ex-vivo expansion and maturation of CD34-positive hematopoietic progenitors optimization of culture conditions.

Mellado-Damas N, Rodriguez JM, Carmona M, Gonzalez J, Prieto J.

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The aim of this study was to look for an ex vivo culture system for clinical application. We evaluated the ex vivo expansion of peripheral blood CD34+ cells in gas-permeable bags and whether or not an exogenous protein source would be required in these kind of cultures. We also evaluated maturation of the cells during culture. Cells were cultured for 15 days in medium supplemented with SCF, G-CSF, IL3 and IL6. The bags supported the expansion of hematopoietic cells in a similar manner to small scale flasks system: (a) the expansion means of total nucleated cells on day +5 were 12.5-fold for bag versus 5-fold for flask, on day +10 were 44.12-fold for bag versus 41-fold for flask and on day +15 were 67.7-fold for bag versus 84.2-fold for flask, (b) the peak values of CFU-GM were reached on day +10 (9.2-fold for bag vs. 12-fold for flask), and (c) maximal expansion of CD15+/CD11b- population occurred on day +10 (517.5-fold for bag vs. 2959.2-fold for flask). So, we did not find any advantages by culturing further than day +10. We subsequently investigated the use of serum-free medium. The study showed better results when we used medium supplemented with autologous plasma versus serum-free system. In summary, these data described a strategy of culture clinically feasible and safe, using gas-permeable bags, and the kinetics and differentiation of neutrophils and neutrophil precursors from selected CD34+ cells in liquid cultures. Ex vivo expansion of this population might result in earlier engraftment as compared with that for selected stem cells alone.

PMID: 10576508 [PubMed - indexed for MEDLINE]

Ann N Y Acad Sci. 1999 Apr 30;872:57-66; discussion 66-70. Related Articles, Links

Further characterization of CD34-low/negative mouse hematopoietic stem cells.

Nakauchi H, Takano H, Ema H, Osawa M.

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We have previously reported that in adult mouse bone marrow, CD34low/- c-kit+ Sca-1+ lineage markers negative (Lin-) (CD34-KSL) cells represent hematopoietic stem cells with long-term marrow repopulating ability whereas CD34+ c-kit+ Sca-1+ Lin- (CD34+KSL) cells are progenitors with short-term reconstitution capacity. To further characterize cells in those two populations, relative expression of various genes were examined by reverse transcriptase polymerase chain reaction (RT-PCR). In CD34-KSL cells, none of the genes studied was found to be expressed with the exception of GATA-2, IL-1R alpha, IL-2R gamma, AIC-2B, c-kit, EPO-R, and c-mpl. In contrast, expression of GATA-1 and all cytokine receptor genes examined except IL-2R beta, IL-7R alpha and IL-9R alpha were found in CD34+KSL. The difference between these two populations was also shown in single cell culture analysis of these cells. When cells were clone-sorted and cultured in the presence of SCF, IL-3 and EPO, CD34-KSL cells required much more time to undergo the first cell division than CD34+KSL cells. Dormancy and random fashion of cell division by CD34-KSL cells were also evident by the analysis of the second cell division, which was found to be delayed and unsynchronous compared with CD34+KSL cells. Clonal culture analysis showed that CD34-KSL cells were more potent in proliferation and multilineage differentiation capacities than CD34+KSL cells. In a paired-daughter cell experiment, 75% of CD34-KSL and 50% of CD34+KSL paired-daughter-derived colonies were nonidentical with wide variety of lineage combinations. Taken together, these data support our previous notion that CD34-KSL cells are at higher rank in hematopoietic hierarchy than CD34+KSL cells. In addition, our results using highly enriched stem cell population directly obtained from mouse bone marrow support the proposed stochastic nature of lineage commitment.

PMID: 10372111 [PubMed - indexed for MEDLINE]

Proc Soc Exp Biol Med. 1990 Oct;195(1):95-9.

Related Articles, Links

Comparative hematopoietic toxicity of doxorubicin and 4'-epirubicin.

OKunewick JP, Kociban DL, Buffo MJ.

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4'-Epirubicin is an anthracycline analog of doxorubicin which has been shown to be similar to doxorubicin in its anti-tumor activity but significantly lower in its cardiotoxicity. Therefore, it has been proposed as a potential clinical substitute for doxorubicin. Using the hematopoietic colony-forming unit, spleen (CFU-S) assay technique, direct comparison was made of the hematopoietic toxicity of the two drugs in vivo in a mouse model, and 4'-epirubicin was found to be significantly (P less than 0.01) less toxic than doxorubicin. On a milligram per kilogram basis, the dose of 4'-epirubicin required to achieve a given level of hematopoietic progenitor cell kill was approximately 50% larger than that required for doxorubicin. Early CFU-S recovery following 4'-epirubicin exposure was also stronger than that achieved following doxorubicin, as was short-term peripheral white blood cell recovery. These findings confirm previous clinical suggestions that the acute toxicity of 4'-epirubicin toward hematopoietic progenitor cells might be less than that of doxorubicin. At the same time, however, when given in doses near their lethal limit, both drugs were shown to induce a chronic hematopoietic suppression. This was evident in the depressed long-term CFU-S levels following high doses of either drug, as well as in chronically depressed white blood cell levels following high-dose 4'-epirubicin.

PMID: 2399266 [PubMed - indexed for MEDLINE]

Science. 1996 Jul 12;273(5272):242-5. Related Articles, Links

Long-term lymphohematopoietic reconstitution by a single CD34-low/negative hematopoietic stem cell.

Osawa M, Hanada K, Hamada H, Nakauchi H.

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Hematopoietic stem cells (HSCs) supply all blood cells throughout life by making use of their self-renewal and multilineage differentiation capabilities. A monoclonal antibody raised to the mouse homolog of CD34 (mCD34) was used to purify mouse HSCs to near homogeneity. Unlike in humans, primitive adult mouse bone marrow HSCs were detected in the mCD34 low to negative fraction. Injection of a single mCD34(lo/-), c-Kit+, Sca-1(+), lineage markers negative (Lin-) cell resulted in long-term reconstitution of the lymphohematopoietic system in 21 percent of recipients. Thus, the purified HSC population should enable analysis of the self-renewal and multilineage differentiation of individual HSCs.

PMID: 8662508 [PubMed - indexed for MEDLINE]

Semin Surg Oncol. 1989;5(6):414-9.

Related Articles, Links

Cancer-induced immunosuppression: implications for therapy?

Pollock RE, Roth JA.

University of Texas M.D. Anderson Cancer Center, Department of General Surgery, Houston 77030.

Cancer-induced immunosuppression can be caused by a variety of effects. These include factors produced by the host in response to the presence of tumor or factors elaborated by the tumor itself. Disseminated tumor can lead to host debility with associated anergy. Some immunosuppressive effects are due to the manner in which the host processes (or fails to process) the tumor as an antigenic stimulus. Lastly, antitumor treatments can have a detrimental impact on host antitumor immunity. Recent research findings from our laboratories implicate surgical stress effects and tumor-mediated production of growth factors such as transforming growth factor beta (TGF-beta) as being important causes of host immune impairment. An accurate understanding of the mechanisms underlying host antitumor immune impairment will be critical in the successful development of immunotherapy strategies for use in the surgical oncology patient.

Publication Types:

- Review
- Review, Tutorial

PMID: 2688031 [PubMed - indexed for MEDLINE]

Oncol Nurs Forum. 1991 Mar;18(2 Suppl):7-15. Related Articles, Links

Current strategies for managing myelosuppression in patients with cancer.

Rostad ME.

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Myelosuppression in patients with cancer is usually the result of tumor invasion of the bone marrow, cytotoxic chemotherapy, or radiation therapy, all of which suppress bone marrow function. Anemia, thrombocytopenia, and neutropenia are the three most clinically significant complications that result from bone marrow depression. Although anemia and thrombocytopenia can produce serious clinical problems, blood-component transfusions--despite having inherent problems of their own--usually are successful in correcting or minimizing these complications. Although neutropenia is manageable in most situations, it remains a serious problem that, at its worst, can progress to life-threatening septicemia. The longer neutrophil counts remain low, the more susceptible patients become to infection by endogenous and exogenous microbial flora. Accordingly, the oncology nurse increases the frequency of patient assessment and monitoring for infection. Control measures are introduced to minimize environmental contaminants. These measures attempt to reduce the incidence of opportunistic infections that frequently occur in patients with severe or prolonged neutropenia and for which antimicrobial therapy is indicated. Implementing specific infection-control interventions and thoroughly educating the patient and his/her family help to limit the clinical problems associated with myelosuppression for most patients.

Publication Types:
- Review
- Review, Tutorial

PMID: 1904577 [PubMed - indexed for MEDLINE]

Int J Hematol. 2000 Jan;71(1):33-9. Related Articles, Links

Thrombopoietin stimulates murine lineage negative, Sca-1+, C-Kit+, CD34- cells: comparative study with stem cell factor or interleukin-3.

Shimomura T, Yonemura Y, Miyazoe T, Miyake H, Kato T, Miyazaki H, Mitsuya H, Kawakita M.

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It has recently been reported that human thrombopoietin (TPO) acts on early hematopoietic progenitor cells. Consequently, we investigated the effects of TPO on murine hematopoietic progenitor cells using lineage negative (Lin-), Sca-1+, c-Kit+ marrow cells from 5-fluorouracil-treated mice. One hundred enriched cells were cultured in suspension with various single cytokines for 5 days. When cultured with the single cytokines as stem cell factor (SCF), TPO, or interleukin (IL)-3, these cells were maintained or had increased by day 5, whereas only a few cells survived in cultures with granulocyte colony stimulating factor, IL-11, or IL-6. We extended the study in serum-free or serum-containing suspension cultures with SCF or TPO. Anti-TPO antibodies did not inhibit the effects of SCF on enriched cells but did inhibit the effects of TPO on those cells. We further examined the effects of TPO, SCF, and IL-3 on other populations of murine hematopoietic progenitor cells. Either TPO or SCF as a single cytokine could maintain murine Lin-, Sca-1+, c-Kit+, CD34- marrow cells, which are the most dormant cells. In addition, IL-3 increased Lin-, Sca-1-, c-Kit+ cells more than did SCF and TPO but did not stimulate Lin-, Sca-1+, c-Kit+, CD34- cells more. These results indicate that TPO as well as SCF may be key regulators in the proliferation of murine hematopoietic early progenitor cells.

PMID: 10729991 [PubMed - indexed for MEDLINE]

Leukemia. 2000 May;14(5):947-8.

Related Articles, Links

Loss of CD38 antigen on CD34+CD38+ cells during short-term culture.

von Laer D, Corovic A, Vogt B, Fehse B, Roscher S, Rimek A, Baum C, Ostertag W.

Publication Types:

- Letter

PMID: 10803533 [PubMed - indexed for MEDLINE]

J Immunother. 1997 May;20(3):165-77. Related Articles, Links

Comment in:
- J Immunother. 1997 May;20(3):178-9.

Reversal of tumor-induced immunosuppression: a new approach to cancer therapy.

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Many studies show defective immune responses in patients diagnosed with cancer. Most of the diverse nonspecific approaches used to stimulate the immune system to recognize and destroy abnormal tumor cells have limited clinical utility. Attempts to identify tumor-specific antigens and to improve the antigen presentation were equally disappointing. It appears that some of these failures can be explained by tumor-induced immunosuppression. A large number of cytokines, hormones, and other molecules secreted by tumors were demonstrated to have immunomodulating properties. The most extensively studied immunosuppressive molecules secreted by tumors are transforming growth factor-beta (TGF beta), interleukin 10 (IL-10), and prostaglandin E2 (PGE2). TGF beta in particular may play a key role in tumor-induced immunosuppression. It is the most potent immunosuppressor described to date, and it has been consistently isolated from variety of tumor cell lines and detected in plasma of tumor-bearing hosts. Level of TGF beta production by tumor cells correlates with their metastatic potential, and TGF beta neutralization not only prevents development of metastases, but also inhibits growth or completely eradicates tumors as diverse as breast cancer, melanoma, and malignant gliosarcoma in animal models. PGE2 may play significant role in early stages of tumor development, promoting the process of tumorigenesis in some tumors. Research on reversal of tumor-induced immunosuppression promises new, more powerful, and less toxic approaches to cancer therapy. Existence of molecule(s) consistently secreted by different types of tumors and responsible for tumor progression raises the possibility of a single, universal assay to monitor progression and recurrence in many malignancies, including those that currently do not have reliable plasma markers.

Publication Types:
- Review
- Review, Tutorial

PMID: 9181454 [PubMed - indexed for MEDLINE]